72. (Unchanged) The method of claim 47 further comprising sensitizing the patient with a therapeutically effective amount of 1-fluoro-2,4-dinitrobenzene prior to administering cyclophosphamide.

74. (Unchanged) The method of claim 47 wherein said adjuvant is *Bacillus Calmette-Guerin*.

75. (Unchanged) The method of claim 47 wherein said administration prolongs survival of said patient.

76. (Unchanged) The method of claim 44, wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly $CD8^+CD4^-$.

77. (Unchanged) The method of claim 47, wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly $CD8^+CD4^-$.

REMARKS

Applicant gratefully acknowledge the courtesy shown by Examiner Ungar and Supervising Patent Examiner Caputo at the personal interview with inventor Dr.

David Berd, expert Dr. Donald Braun, licensee's representative Dr. Ernest Yankee, Dr. Anna Lövqvist of Darby & Darby, and the undersigned. Applicant especially appreciates the Examiner's helpful suggestions on claim amendments, as well as the fruitful discussion about art to be submitted in support of the non-obviousness of the instant patent application.

The claims have been amended to more particularly recite the subject matter of Applicants' invention. More specifically, claim 43 has been amended to recite that the composition of the invention elicits, when administered together with an adjuvant, an inflammatory immune response against the tumor. Support for this amendment can be found throughout the application, *e.g.*, in Examples 2 (p. 21, ll. 21-27) and 3 (p. 22, l. 22 to p. 23, l. 4). In addition, to concord with the wording of claim 44, claims 43 and 47 have been amended to recite that a response is elicited in "the patient" instead of in "the human."

This submission is in response to the Official Action dated November 29, 2000. Claims 43 and 47 have been amended. Claims 43-44, 47, 49-62, 64-72, and 74-77 are pending. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 43, 49-51, and 54-55 remain rejected for allegedly not being enabled by the disclosure (see paragraph No. 4 or the Office Action). According to the Examiner, the claims are not drawn to a component of a vaccine that upon addition of an adjuvant will elicit an immune response but rather specifically recite the limitation that upon injection the composition (without adjuvant) elicits an inflammatory immune response.

During the recent interview mentioned above, the Examiner suggested removal of the functionality limitation of this claim as one strategy to address this rejection. However, in order to more particularly recite the subject matter of Applicants' invention, Applicant has amended claim 43 to recite that the composition of the invention elicits, when administered together with an adjuvant, an immune response. In a previous Office Action, the Examiner stated that the specification enables a method for treating a malignant tumor in a human patient comprising administering the composition of claim 43 (*i.e.*, haptenized autologous non-melanoma tumor cells) and BCG (Office Action dated April 28, 1999; paragraph No. 6). Moreover, this recitation is supported throughout the specification. For instance, Examples 2 and 3 report eliciting a striking inflammatory response when the composition of the invention was administered together with the adjuvant BCG. Claims 49-51 and 54-55 depend from claim 43.

Accordingly, in view of the above amendment, Applicant respectfully requests withdrawal of this rejection.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

In this section, Applicant addresses in turn each obviousness rejection maintained by the Examiner in the Final Office Action. However, first, Applicant would like to address the key feature of these obviousness rejections, namely the teachings of the abstract of Berd et al. (Proc AACR 1989:30:382; hereinafter "Berd 1989").

1. Teachings of Berd 1989

In all of the rejections, the Examiner relies on the Berd 1989 abstract as an allegedly successful example of treatment of melanoma by administration of DNP-conjugated autologous melanoma cells in connection with BCG and a preceding dose of cyclophosphamide. The Examiner also contends that it would have been expected that the autologous irradiated melanoma, lung, colon, kidney, and colon cancer cells of Wiseman (discussed below) would be successfully substituted for the melanoma cells of Berd 1989 to treat other cancer types (Office Action, bridging paragraph between pp. 5 and 6). However, both of these conclusions depend on according more weight to the Abstract than one of ordinary skill at the time of the invention would have given it. As set forth by the Braun Declaration accompanying this response, Berd 1989 does not describe a successful immunotherapy for melanoma (Braun Declaration, paragraph 7). On the contrary, it represents a preliminary result that raises more

questions and ambiguities than it answers. Early animal work on tumor immunotherapy could not establish whether similar approaches could work in humans (Braun Declaration, paragraph 8). The Abstract fails to provide a definitive protocol that would permit one to repeat the work, determine whether this approach elicited an immune response to unmodified cells, or establish that it achieved any clinical benefit (Braun Declaration, paragraphs 9, 10, 11).

Three basic criteria ***must*** be met to establish a *prima facie* case for obviousness under 35 U.S.C. § 103(a). First, there must be some suggestion or motivation to modify what is taught in a reference or to combine reference teachings. Second, there must be a reasonable ***expectation of success***. Finally, the prior art reference or combination of references must teach all of the claim limitations. Both the motivation and the reasonable expectation of success must be found in the prior art, not in applicant's disclosure. *See*, M.P.E.P. § 2143, *citing In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As explained in detail below, the present Office Action fails to establish a *prima facie* case for obviousness under these requirements. In particular, since Berd 1989 fails to provide any expectation of success, *i.e.*, clinical benefit, using the haptenized tumor cell approach in ***melanoma*** patients, this reference is completely irrelevant in providing any expectation of success for such an approach in ***other types*** of cancer. Since no other reference cited by the Examiner makes up for this

fundamental flaw, nor the combination of them (see below), obviousness does not obtain.

2. The rejection over Murphy, Berd 1989, Geczy, and the Antibody Patents

Claims 47, 65-72 and74-77 remain rejected as allegedly being obvious over Murphy et al. (Lab Invest 1990;62:70A; hereinafter "Murphy"), in view of U.S. Patent No. 5,702,704 (hereinafter "'704 patent"), U.S. Patent No. 5,626,843 (hereinafter "'843 patent), U.S. Patent No. 5,008,183 (hereinafter "'183 patent"), or U.S. Patent No. 4,232,001 (hereinafter "'001 patent") (hereinafter collectively "the Antibody Patents"); Berd 1989, and Geczy et al. (J Immunol. 1970;19:189-203, hereinafter "Getzy") (see paragraph No. 5 of the Office Action).

Briefly, the above described features in ***Murphy*** relied upon by the Examiner are all disclosed by Berd 1989. In these aspects, therefore, Murphy is cumulative to Berd 1989, which teachings and deficiencies are described in the enclosed Braun Declaration, and discussed above. Although Murphy does describe various biomolecular features of tumor-adhesion proteins and the tumor-infiltrating T lymphocytes etc., the reference fails to compensate for the lack of teachings in Berd 1989 with respect to any ***clinically significant*** tumor regression being observed, as well as the numbers and route of administration (Braun declaration, ¶¶9 and 11). Thus, similar to Dr. Braun's analysis of Berd 1989 (¶11), one of ordinary skill in the art would have presumed that Murphy's haptenized tumor cells and BCG had been

injected intratumorally, and that the BCG was thereby responsible for the observed, clinically non-significant, tumor responses. Accordingly, Murphy suffers from the same lack of expectation of success for the haptenized-tumor-cell approach in melanoma, even more so in the case of non-melanoma tumors, as Berd 1989.

The teachings and deficiencies of ***Geczy*** have been discussed in Applicant's previous amendment, filed September 22, 2000, on pages 11-12, paragraphs 3.b.iii. Briefly, Geczy indeed teaches the equivalency of CDNB and FDNB for the induction of DTH as stated by the Examiner, but proposes that direct haptenization of lymphocytes is necessary for lymphocyte transformation, *i.e.*, reactivity with hapten. Thus, to the extent that the teachings of Geczy relates to those of Berd 1989 and/or Murphy, they diverge and teach away, precluding any combination. Geczy relates to ***anti-hapten*** responses, which in the settings of Berd 1989 or Murphy would hardly be relevant for ***anti-tumor*** responses elicited by haptenized tumor cells, but only for immune response towards the haptenized tumor cell vaccine itself.

With respect to ***The Antibody Patents***, their teachings and deficiencies were also discussed in the previous amendment dated September 22, 2000, pages 10-11, paragraph 3.b.ii. Briefly, these patents describe conventional methods for generating antigen-specific antibody responses. Accordingly, The Antibody Patents teaches nothing about anti-tumor immunity, which requires an protective immunity, *i.e.*, a T cell response. Neither do The Antibody Patents teach six administrations or

immunizations of haptenized tumor cells (or any pathogenic antigen) to humans at spaced intervals for the treatment of cancer, a teaching that is lacking in he other references cited in this rejection as well.

When combining these patents with Geczy, one might at best conclude that haptenization of the already immunogenic antigens described in The Antibody Patents would elicit, in addition to an antigen-specific antibody response, an ***anti-hapten*** response should the haptenized antigens come into direct contact with lymphocytes. Adding Berd 1989 and/or Murphy to the combination merely reinforces the divergence of this combination from the claimed invention, since the combined references, in view of the level of skill in the art at the time, would suggest that no clinically significant anti-tumor responses are elicited by the administration of haptenized tumor cells together with BCG; only an anti-hapten response combined with a non-clinically significant tumor regression resulting from the presumed intratumoral injection of BCG. Therefore, in conclusion, the combination of references would provide no expectation of clinical success in treating any tumor, particularly a non-melanoma tumor, using the methods of claimed invention.

The Examiner cited two cases to support her analysis of obviousness. In particular, the Examiner points out that "[t]he test for obviousness...is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 208 USPQ 871, 881 (CCPA 1981) (Citations omitted). However, the Examiner must consider the references for all that they teach; it is

impermissible to consider a reference in less than its entirety, or to disregard disclosures that diverge and teach away. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1993), *cert. denied* 469 U.S. 851 (1984). Moreover, the prior art, and not the disclosure in the application, must both suggest the invention and provide a reasonable expectation of success in achieving it. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991).

Correctly applying the foregoing legal principles, one arrives at the distinct impression that the combined teachings of the references neither (1) suggest the invention, nor (2) provide a reasonable expectation of success. Berd 1989 (and by extension Murphy 1990) are inadequate to suggest adapting the haptenization strategy to other tumor immunotherapies, much less provide a reasonable expectation of success. Taken together, as the Examiner points out that the references must be considered, the references do not render the claimed invention obvious.

3. The rejection over Berd 1989, the Antibody Patents, and Geczy

Claims 47, 65-72, and 74-77 remain rejected as allegedly being obvious over Berd 1989 in view of the Antibody Patents and Geczy (see paragraph 6 of the Office Action). The Examiner maintained this rejection for the same reasons described in the above rejection.

As outlined in the section above, the combination of Berd 1989 (and/or Murphy), the Antibody Patents, and Geczy, fails to render the instant invention obvious. One of ordinary skill in the art would not have had a reasonable expectation

of success in eliciting an anti-melanoma response using haptenized tumor cells in conjunction with BCG based on the combined teachings of these references, much less any expectation of success should treatment of any other tumor than melanoma have been considered.

4. The rejection over Berd 1989, the Antibody Patents, and Geczy in view of Wiseman

Claims 43, 44, 47, and 49-62, 64-72, and 74-77 remain rejected as allegedly being unpatentable over Berd '89 in view of the Antibody Patents, and Geczy, in further view of Wiseman et al. (West J Med 1989;151:283-288, hereinafter "Wiseman"). The Examiner contends that "Wiseman clearly showed that autologous irradiated melanoma, lung, colon, and kidney cancer were successfully used for successful immunological treatment of those cancers and it would have been expected that these cell types, already known in the art to be useful as immunogenic cancer treatments would be successfully substituted for the melanoma cells of Berd [1989] in order to treat the other cancer types" (Office Action, paragraph bridging pages 5 and 6).

As discussed in the previous amendment dated September 22, 2000 (p. 17, 1st full paragraph), ***Wiseman*** teaches an alternative form of immunotherapy that depends on the route of administration: intralymphatic immunization. This alternative, which Wiseman indeed reports favorably, in no way suggests a deficiency or problem that would lead one of ordinary skill in the art to seek an alternative immunization

strategy. On the contrary, it leads away from the claimed invention, thus precluding combining this reference in making the rejection. One of ordinary skill in the art would, when faced with the Wiseman reference on one hand and the combination of Berd 1989, The Antibody Patents, and Geczy on the other, the latter suggesting that no success (*i.e*, anti-tumor response) was to be expected by using haptenized autologous melanoma cells, merely an anti-hapten response and a clinically non-significant tumor regression due to intratumoral injection of BCG, simply choose the reportedly successful approach of Wiseman.

5. The rejection over Berd 1989, the Antibody Patents, Geczy, and Berd 1983

Claims 43, 44, 47, and 49-62, 64-72, and 74-77 remain rejected as allegedly being unpatentable over Berd '89 in view of the Antibody Patents, and Geczy, in further view of Berd et al., (PASCO 1983;2:56, hereinafter "Berd 1983) (Office Action, paragraph No. 8). With respect to the arguments set forth in the previous amendment, the Examiner alleges that Applicant was arguing the Berd 1983 individually without clearly addressing the combined teachings. Applicant respectfully disagrees. Applicant chose to, instead of repeating arguments already made in the amendment, discuss the entirety of the teachings of Berd 1983 before adding this reference to the combination of Berd 1989, the Antibody Patents, and Geczy (see amendment dated September 22, 2000, page 18, section 3.g). In doing so, it is clear that Berd 1983 adds nothing to the combination of Berd 1989, The Antibody Patents,

and Geczy, which fails to provide any reasonable expectation of success as discussed above.

Berd 1983 teaches the intradermal administration of autologous tumor cells to six cancer patients, five suffering from melanoma and one from breast cancer, and reports DTH responses against tumor cells in three out of the five evaluated patients. Note that Berd 1983 is silent with respect to the tumor type of the patients DTH tested, as well as whether the single breast cancer patient was among the 3 patients (50%) showing a DTH response. Even assuming that the breast cancer patient was among the three, the addition of Berd 1983 to the combination of reference would not provide a reasonable expectation that a ***haptenized*** tumor cell vaccine, whether based on melanoma or breast cancer cells, would elicit a clinically significant anti-tumor response.

6. The rejection over Berd, the Antibody Patents, Geczy, and Sanda and Moody

Claims 43, 44, 47, and 49-62, 64-72, and 74-77 remain rejected as allegedly being unpatentable over Berd '89 in view of the Antibody Patents, Geczy, in further view of Sanda et al. (J Cellular Biochem 1993;suppl.17D:120, hereinafter "Sanda") and Moody et al. (J Urol 1991;145:293A, hereinafter "Moody") (Office action, section 9).

Berd 1989, The Antibody Patents, and Geczy are discussed individually, as well as in combination, in the sections above.

Sanda teaches a method for transducing human prostate cancer cells with a particular retroviral vector. The method was reportedly successful for transfecting the cells, and Sanda suggest that this approach may be feasible in gene therapy of prostate cancer. Although Sanda fails to provide any description on just how his approach would be used in gene therapy and why, the general approach in gene therapy is to administer a gene, locally or systemically, to a patient in an attempt to transfect cells *in vivo* for some therapeutic purpose. This approach is wholly unrelated to any immunotherapeutic method for cancer treatment, and therefore cannot add anything to the combination of references cited in this rejection.

Moody teaches a immunotherapy method based on lymphokine expression in which rat prostate tumor cells were transfected with cDNA encoding IL-2 and IL-4, the transfected tumor cells administered to rats, and tumor immunity observed in the treated rats as compared to controls.

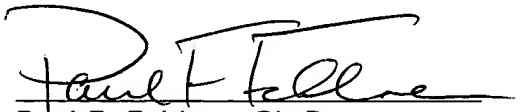
When added to the combination of Berd 1989, The Antibody Patents, and Geczy discussed above (to which Sanda adds nothing), Moody's approach, promising in an animal model, merely contributes with the notion that prostate cancer cells expressing cytokines is an alternative immunotherapy regimen yet to be evaluated in patients. The lack of reasonable success suggested by Berd 1989 for haptenized tumor cells, evident from the Braun Declaration enclosed herewith, is not compensated for by Moody or any other of the cited references, nor by the combination of these references.

Thus, in view of the above arguments, Applicant respectfully requests reconsideration and withdrawal of all of the remaining obviousness rejections above. Without a reasonable expectation of success for the claimed invention, clearly not provided by any combination of the above cited references, obviousness does not obtain.

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Paul F. Fehlner, Ph.D.
Reg. No. 35,135
Attorney for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700

M:\1225\0C674\AL1009.WPD

EXPRESS MAIL CERTIFICATE

Date 5/29/01 Label No. EK706741126US

I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

B Beck L Beck

Name (Print) Signature

PLEASE CHARGE ANY DEFICIENCY UP TO $300.00 OR CREDIT ANY EXCESS IN THE FEES DUE WITH THIS DOCUMENT TO OUR DEPOSIT ACCOUNT NO. 04-0100

JC76 MAY 29 2001 PATENT A

Customer No.: 07278

PATENT TRADEMARK OFFICE

Docket No.: 1225/0C674

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED
JUN 0 1 2001
TECH CENTER 1600/2900

In re Application of: David BERD

Serial No.: 08/203,004 Art Unit: 1642

Confirmation No.:

Filed: February 28, 1994 Examiner: S. Ungar

For: COMPOSITION AND METHOD OF USING TUMOR CELLS

MARK-UP FOR AMENDMENT OF MAY 29, 2001
PURSUANT TO 37 C.F.R. § 1.121

Hon. Commissioner of Patents
Washington, DC 20231

Claims:

43. (Amended) A composition comprising human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein;

said composition eliciting, when administered together with an adjuvant, an inflammatory immune response against the tumor of said [human] patient, wherein said tumor is not melanoma.

47. (Amended) A method of treating a malignant tumor in a human patient comprising co-administering to the patient

(a) a composition comprising a therapeutically effective amount of human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein; and

(b) an adjuvant;

wherein said composition elicits at least one of the following upon administration to said patient with the adjuvant: an inflammatory immune response against the tumor of said [human] patient; a delayed-type hypersensitivity response against the tumor of said [human] patient and activated T lymphocytes that infiltrate the tumor of said [human] patient; and

repeating said administration at least six times at spaced apart intervals.

Respectfully submitted,

Dated: May 29, 2001

Paul F. Fehlner, Ph.D.
Reg. No. 35,135
Attorney for Applicant(s)

DARBY & DARBY P.C.
805 Third Avenue
New York, New York 10022
212-527-7700